1: Gene Ther 2001 Jul;8(13):987-98

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A transcriptional feedback loop for tissue-specific expression of highly cytotoxic genes which incorporates an immunostimulatory component.

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Related Resources

Transcriptional targeting of cytotoxic genes is an important way to control toxicity associated with gene transfer therapies, but supposedly, tissue-specific promoters are often either very weak and/or leaky. In addition, the phenotypic leakiness of such tissue-specific promoters is dependent upon the toxicity of the gene being used. Therefore, we devised a transcriptional feedback loop to restrict gene expression of very potent genes to melanoma cells. We screened different elements of the human tyrosinase promoter to find one which gave no detectable expression in non-melanoma cells but was active in melanoma cell lines. This weak, but highly tissue specific, element (Tyr-300) was then used as the basis for a transcriptional amplification feedback loop in which a consensus heat shock element (HSE) was cloned upstream of Tyr-300. The cytotoxic gene was cloned downstream of the HSE-Tyr-300 element along with a mutated form of the heat shock factor-1 (HSF-1) transcription factor, which no longer requires cellular stress to activate its trimerisation, nuclear localisation and transcriptional activation properties. Low levels of expression from Tyr-300 initiated expression of both the cytotoxic and the HSF-1 genes in melanoma cells. Gradual build up of HSF-1 amplified expression through binding to the HSE to give levels of cytotoxicity similar to that provided by a CMV promoter. However, no leakiness was observed in multiple non-melanoma cell lines tested. In addition to amplifying low levels of weak tissue-specific expression, the use of HSF-1 also leads to activation of endogenous stress-related genes such as hsp70. Induction of these genes, in the presence of cell killing by the cytotoxic gene, is a highly immunostimulatory event which enhances the antitumour vaccination effects of direct tumour cell destruction. Having demonstrated the compatibility of the component elements in plasmid form, we incorporated the feedback loop into a hybrid LTR-modified retroviral vector and confirmed that the system can be effective in the form of a viral vector. The format of the feedback loop described here could be exploited for any tissue type in which

a highly tissue-specific element can be identified but which is itself too weak to be effective therapeutically.

PMID: 11438833 [PubMed - indexed for MEDLINE]

1: Mol Med Today 1998 Feb;4(2):84-92 Related Articles, Links

Strategies for achieving multiple layers of selectivity in gene therapy.

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Here we review the progress towards the development of targeted vectors for direct in vivo delivery in gene therapy. Currently, there are many separate approaches. These include: simple physical/anatomical localization of administration of the vector at the site where gene transfer is required; exploitation of natural tropisms of plasmid, viral and cellular vectors; and the use of molecular engineering to change the specificity of proteins and nucleic acids so that they specifically recognize target ligands expressed on/in the target cells. Unfortunately, each of these approaches is usually imperfect by itself. However, combinations of these strategies might produce vectors in which several layers of imperfect targeting give an overall level of specificity that can justify systemic delivery of vectors to treat human disease.

Publication Types:
- Review
- Review, Tutorial

PMID: 9547795 [PubMed - indexed for MEDLINE]

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	DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=AND		
L12	L11 same (promoter)	41	L12
L11	(vector or (nucleic adj acid)) same ((amplification) same (activator))	81	L11
L10	L2 and (HSE and HSF)	2	L10
L9	L2 and ((amplification) same (transcription adj activator))	0	L9
L8	L2 same ((amplification) and (transcription adj activator))	0	L8
L7	L2 same ((amplification) same (transcription adj activator))	0	L7
L6	L4 and (HSF)	9	L6
L5	L4 and (HSF-1)	0	L5
L4	L2 and (HSE or (heat adj shock))	959	L4
L3	L2 and (amplification adj promoter)	10	L3
L2	((tissue or cell or tumor or tumour) adj specific) adj promoter	4358	L2
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END OF SEARCH HISTORY